REMARKS

Introduction

Claims 1-11 are pending in the application. Claims 12-20 have been cancelled without prejudice to the subject matter disclosed therein. Applicant expressly reserves the right to pursue the subject matter of the cancelled claims in this application or in another application.

At the outset, in order to avoid any misunderstandings, the Applicant wants to draw attention to the fact that the Examiner repeatedly wrote "PEG/mg" as a unit of the specific activity of alpha-1-antitrypsin. We assume the Examiner meant "PEU/mg" (plasma equivalent unit/mg) as written in the application. Otherwise, this could lead to misunderstanding as Taniguchi et al. (US 6,284,874; alleged to anticipate most claims of the present application) uses PEG, i.e. poly-ethylene-glycol for the precipitation of alpha-1-antitrypsin.

Rejections under 35 U.S.C. §112

Claim 12 is rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement (page 2). Applicant traverses. To expedite prosecution, claim 12 has been cancelled, and the rejection therefore rendered moot.

Claims 12-20 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. (page 8). Applicant traverses. To expedite prosecution, claims 12-20 have been cancelled, and the rejection therefore rendered moot.

Claims 1-5, 9-11, 13-17 are rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. Applicant traverse. To expedite prosecution, claims 13-17 have been cancelled, and the rejection with respect to these claims therefore rendered moot.

Concerning claims 1-5 and 9-11, the Examiner asserts that it would require undue experimentation by a person of ordinary skill in the art to ascertain which concentrations, incubation

time and temperatures greater than the values claimed as lower boundaries will allow a functionally active alpha-1-antitripsin (A1AT) to be obtained.

Applicant respectfully traverses. A person of ordinary skill would begin with the successful values given or apply small variations and he will succeed in obtaining A1AT having a purity > 90% and an activity of 0.8 PEU/mg (plasma equivalent unit/mg). On the other hand, an expert in the art would not apply, e.g., 30% (w/w) tri-n-butyl-phosphate during the S/D treatment for at least two reasons: (i), he or she knows this would be a vast excess of agents, which could be a waste of these chemicals and (ii) it would cause additional unnecessary workload during their removal.

Further, a person of ordinary skill would not apply a temperature of 90°C, during incubation as it is well known that proteins are subject to thermal denaturation. Thus, he or she would rather increase the temperature beginning near the exemplified values. He or she would probably apply 30°C, 40°C and 50°C and would easily find an optimal temperature range to work at. The example itself discloses higher values for most of the disputed parameters. Example 1 discloses to operate the invention at 1% (w/w) Triton (compared to 0.1% Triton of claim 4), 0.3% (w/w) tri-n-butyl-phosphate (TnBP) (compared to 0.03 % tri-n-butyl-phosphate of claim 4), an incubation time of 4 hours (compared to 1 hour of claim 4), an incubation temperature of 20°C (compared to 15°C of claim 4), a salt concentration of 1M (compared to 0.5M of claim 5) during salting out.

In view of the above, this rejection should be withdrawn because an example disclosing sufficient parameters is presented. Additionally, those skilled in the art are generally sufficiently skilled, as the Examiner admits (page 6; "The relative level of skill in the art is very high."), and possess enough knowledge to estimate reasonable ranges of workability. There is no undue experimentation required to practice the invention as claimed.

This is believed to be a full and complete reply which overcomes the rejections and/or renders them moot. Accordingly, the rejections under §112 are improper and their withdrawal is respectfully requested.

Rejection under 35 U.S.C. §102

The Examiner has rejected claims 12-18 and 20 under 35 U.S.C. §102(b) in view of Mattes et al. Applicant traverses. To expedite prosecution, claims 12-18 and 20 have been cancelled, and the rejection therefore rendered moot.

The Examiner has rejected claims 1-5 and 9-11 under 35 U.S.C. §102(b) in view of Taniguchi et al. The applicant respectfully traverses.

Taniguchi et al. teach (example 1) a plasma fraction to be solubilized in WFI (water for injection), precipitation of A1AT by addition of PEG and $ZnCl_2$, applying of the resolubilized precipitate to a QAE anionic exchange chromatographic column. After elution the solution was concentrated, S/D treated for virus inactivation and applied to a copper-chelating medium. The A1AT adsorbed medium was washed with a mixture of NaCl, sodium phosphate and imidazole. A1AT was eluted, ultra- and diafiltrated, applied to a second QAE-chromatography medium, washed, eluted and again diafiltrated.

The claimed invention is unexpectedly more simple and does not require PEG/$ZnCl_2$ precipitation, work up of the precipitate and resolubilization. Neither a metal chelate chromatography is used nor mentioned according to the invention. However, this seems to be an essential step for the method of Taniguchi et al.

The Examiner alleges that the washings with 150 mM NaCl and 500mM NaCl performed on the respective material will correspond to the salting out step of the present invention as a material inherent property. The Examiner asserts that "[e]ven if Taniguchi et al. do not explicitly state that adding NaCl will salt out the detergents, the 'salting out' process would inherently occur since the salt concentration of the A1AT solution was increased by adding NaCl

solution (page 12). The Examiner seems to interpret "salting out" as any increase in salt concentration of any salt. However, this not the case. Salting out is known to require a phase separation and depends on concentration and type of salt. Sodium citrate as used in the present application will require a different concentration for a phase separation than sodium chloride, which is used by Taniguchi et al. for washing adsorbed A1AT. Assuming a phase separation would occur during washing of the chromatographic medium, clogging of the column would be almost unavoidable and result in heavily handicapped operation or even make operation impossible. This did not happen in Taniguchi's method, which makes it clear that since no phase separation occurred, no salting out step was performed.

As discussed above, the process of "salting out" requires a phase separation that is dependent on the particular salt and concentration. Therefore, simply increasing the salt concentration does not **necessarily** result in a phase separation or "salting out." For at least this reason, increasing the salt concentration does not inherently result in "salting out" and Taniguchi et al. does not teach all the features of the present invention. In view of the above, Applicant respectfully requests withdrawal of the rejection of claims 1-5 and 9-11 in view of Taniguchi et al.

An additional indication for the difference between Taniguchi's washing and the salting out of the present application is the fact that A1AT binds to the metal chelate medium of Taniguchi. This interaction definitely interferes with the conditions in solution resulting in facilitation of washing and prohibition of formation of a two or multi-phase system. In other words, to generate an additional phase (i.e. by salting out) while A1AT is bound to the chelate medium, it is necessary to apply salt in higher concentrations compared to starting solution. This means, even assuming the capabilities of sodium citrate and sodium chloride for salting out would be identical, that, at a concentration of 500mM salt (which represents the higher concentration of Taniguchi's washing solution) no generation of an additional phase occurs compared to the salting out step of the claimed method where this concentration represents the lower boundary at which phase separation occurs.

Additionally, the method of the present invention teaches in paragraph [0044], that the A1AT solution is diluted by a 1.5M citrate solution to end up at a total citrate concentration of

greater than 500mM (i.e. 1000mM) citrate (as required by claim 5 for example) for the total volume of A1TA solution plus citrate solution. On the other hand, Taniguchi et al. teaches the concentration of the initial washing solution **before** entering the chromatographic column to be 500mM NaCl. The actual concentration inside the column cannot readily be determined (total volume of the column minus the (swollen) resin volume, or total volume of the column minus the (swollen) resin volume minus the volume of adsorbed A1AT (plus other unknown compounds, or other determinations methods for void volume); in any case the salt concentration inside the column will be less than 500 mM NaCl. Thus, Taniguchi discloses a washing step not a salting out step as the claims require.

It is apparent that washing of A1AT adsorbed on a metal chelating medium is not comparable to the salting out step of claim 1c). Thus, Taniguchi et al. neither anticipates nor renders obvious the subject matter of claims 1-5 and 9-11.

Rejection under 35 U.S.C. §103(a)

Claims 6-8 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious in view of Taniguchi *et al.* and Isaksson *et al.* Applicants respectfully traverse. As discussed above, Taniguchi *et al.* does not disclose the "salting out" of the detergents according to the claims. The secondary reference fails to remedy this omission. For at least this reason, the rejection of claims 6-8 under 103(a) is improper and its withdrawal is respectfully requested.

Furthermore, Isaksson teaches that it is possible to reduce the content of solvents and detergents used for virus inactivation (S/D treatment) to a final concentration below 5 ppm by salting out solvents and detergents using citrate and other salts with or without the addition of soybean oil. The Examiner alleges that Isaksson teaches the process to be applicable to any plasma protein. Isaksson gives on page 6, lines 15-20 a listing of 6 examples where the disclosed method is applicable. The examples are factor VIII, factor IX, albumin, transferrin, alpha-1-acid glycoprotein and antithrombin-III, none of which is alpha-1-antitrypsin. However, the claimed invention is directed to alpha-1-antitrypsin, which is not mentioned in Isaksson et al.

Isaksson also mentions that anthithrombin-III used during experimentation was produced by use of heparin sepharose gel. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to substitute the anionic-exchange column of Taniguchi et al. by the heparin sepharose gel of Isaksson's antithrombin production. It is very doubtful that a person of ordinary skill would perform this substitution, because a person of ordinary skill would not incorporate a purification step used for the production of a different product (antithrombin). A person of ordinary skill in the art would know that steps known for the production of one protein can usually not be applied to the production of another protein so easily as the Examiner suggests. Furthermore, the skilled person did not have any incentive to perform such a substitution.

In view of the above, there is simply no evidence that these substitutions would be obvious or reasonably expected to be successful. Applicant respectfully asserts that the rejection under 35 U.S.C. §103(a) is improper and requests that this rejection be withdrawn.

CONCLUSION

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is hereby invited to telephone the undersigned at the number provided.

The Commissioner is authorized to charge any deficiency in any patent application processing fees pursuant to 37 CFR § 1.17, including extension of time fees pursuant to 37 CFR § 1.17(a)-(d), associated with this communication and to credit any excess payment to Deposit Account No. 22-0261.

Dated: March 10, 2009

Respectfully submitted,

By /Matthew E. Kelley/
Matthew E. Kelley
Registration No.: 55,887
VENABLE LLP
P.O. Box 34385
Washington, DC 20043-9998
(202) 344-4000
(202) 344-8300 (Fax)
Attorney/Agent For Applicant

#322446v4